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HEALTH TECHNOLOGY BRIEFING SEPTEMBER 2019

Ixazomib citrate for newly diagnosed multiple myeloma inelgible for autologous stem cell transplant– maintenance therapy

NIHRIO ID	13276	**NICE ID**	9778
Developer/Company	Takeda UK Ltd	**UKPS ID**	642371

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Ixazomib citrate is in development for the maintenance treatment of adults with newly diagnosed multiple myeloma (NDMM) that are ineligible for an autologous stem cell transplant (ASCT). It would be given as monotherapy for maintenance as part of the initial line of therapy for such patients. MM is a rare, incurable cancer of the plasma cells in the bone marrow (the spongy tissue at the centre of some bones). MM is the second most common blood cancer in the UK. Symptoms of MM may include bone pain, fractures, body weakness, malaise, bleeding, anaemia and infections. MM treatment often involves a stem cell (or bone marrow) transplant that requires medications before and after to improve the success of treatment.

Ixazomib citrate is a novel oral medicinal product that is already licensed in the UK for the treatment of MM in patients who have received at least one prior therapy (in combination with lenalidomide and dexamethasone). Ixazomib citrate offers the potential advantage over similar medicines in its class of being more effective in its anticancer activity, reduced side effects and more convenient to administer (through its weekly oral dosing). If approved as maintenance therapy for NDMM patients, ixazomib maintenance has the potential to prolong the time patients live without their disease getting worse (progression free survival) as well as offering more convenient oral dosing that allows long term administration and improvement of patients' quality of life.

PROPOSED INDICATION

Multiple myeloma (newly diagnosed) - maintenance treatment following first line induction therapy of adult patients who are ineligible for autologous stem cell transplant (ASCT).[a]

TECHNOLOGY

DESCRIPTION

Ixazomib citrate (Ninlaro; MLN 9708) is a second-generation boronate proteasome inhibitor (PI) and is a prodrug that becomes quickly converted to its active metabolite, ixazomib, after administration.[1-4] Ixazomib citrate is an N-capped dipeptidyl leucine boronic acid which reversibly inhibits the chymotrypsin-like (CT-L) proteolytic (β5) site of the 20S proteasome to induce accumulation of ubiquitinated proteins, which ultimately leads to myeloma cell death.[1]

Ixazomib citrate, given as monotherapy, is intended for the maintenance treatment of adult patients with newly diagnosed multiple myeloma (MM) who are ineligible for ASCT[b] and have completed first line induction therapy and registered a major response - defined as complete response (CR), very good partial response (VGPR), or partial response (PR)[5] In the phase III, randomised, double-blind, placebo-controlled, multicentre study clinical trial (NCT02312258), ixazomib citrate 3 mg capsule is administered orally once on days 1, 8 and 15 in a 28-day cycle for cycles 1 through 4 and if tolerated during the first 4 cycles, is escalated to 4 mg beginning with cycle 5 day 1, or will otherwise remain at 3mg if the patient is not dose escalated. The treatment period will be approximately 24 months (equivalent to 26 cycles) or until patients experience progressive disease or unacceptable toxicity, whichever occurs first.[5]

INNOVATION AND/OR ADVANTAGES

Ixazomib citrate represents the first oral proteasome inhibitor to be evaluated in MM clinical trials.[2,4] Ixazomib citrate also exerts a time-dependent reversible proteasome inhibition but the proteasome dissociation half-life (t½) for ixazomib citrate was found to be approximately six times faster than that of bortezomib (t½ 18 minutes versus 110 minutes).[2,4] According to expert opinion, the oral route of administration and good safety and efficacy profile are characteristics that provide a rationale for its role in the maintenance setting.[4,6] Oral dosing offers convenience advantages for patients and facilitates long term administration.

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Ixazomib citrate in combination with lenalidomide and dexamethasone is licensed in the EU/UK for the treatment of adult patients with MM who have received at least one prior therapy.[3,7] The most common side effects (all-grade adverse event) with ixazomib citrate taken together with lenalidomide and dexamethasone (seen in more than 1 in 5 people) were diarrhoea, constipation, thrombocytopenia (low blood platelet counts), neutropenia (low levels of neutrophils, a type of white blood cell), peripheral neuropathy (nerve damage in the hands and feet causing tingling or numbness), nausea (feeling sick), peripheral oedema (swelling, especially of the ankles and feet), vomiting and nose and throat infection. Similar side effects were seen when lenalidomide and dexamethasone were used without ixazomib citrate.[7]

A phase III clinical trial for ixazomib citrate as monotherapy has been completed (results published) for the maintenance therapy of patients diagnosed with MM following ASCT

[a] Information provided by Takeda UK Ltd
[b] Information provided by Takeda UK Ltd in UK Pharma Scan

(TOURMALINE-MM3, NCT02181413).[8] This trial is similar to the TOURMALINE MM4 study which is the subject of this briefing, but in patients who have had an ASCT. In the TOURMALINE-MM3 trial, the most common haematological adverse events were neutropenia, thrombocytopenia, and anaemia whereas the most common non-haematological adverse events were infection, gastrointestinal disorders, and rash.[9] Additionally, ixazomib citrate is being studied in phase III trials for newly diagnosed MM (NDMM) in combination with lenalidomide and dexamethasone (TOURMALINE-MM2, NCT01850524); as a doublet with dexamethasone in relapsed or refractory Systemic Light Chain Amyloidosis (TOURMALINE-AL1, NCT01659658) and as a doublet with dexamethasone in a phase II/III clinical trial for relapsed/refractory RRMM patients who have received at least 2 lines of prior therapy and are refractory to lenalidomide (TOURMALINE-MM5, NCT03170882).[10]

Ixazomib citrate was designated an EU orphan drug by the EMA in September 2011 for the treatment of MM.[11]

PATIENT GROUP

DISEASE BACKGROUND

MM is a rare, incurable disease characterised by uncontrolled proliferation of monoclonal plasma cells in the bone marrow, resulting in the over-production of monoclonal immunoglobulin, immunosuppression, osteolysis and end-organ damage.[12] The disease is characterised by cycles of response and progression. With increasing lines of therapy, there is a decreasing duration of response and ultimately development of refractory disease, therefore the first remission has the longest duration potential, making it critical for long-term patient outcomes.[13]

The cause of MM is unknown, but is closely associated with a condition called monoclonal gammopathy of unknown significance (MGUS). Estimates suggest approximately 1 in every 100 people with MGUS go on to develop MM on an annual basis.[13] Additional risk factors for MM include age, gender, and ethnicity. Cases affecting those under 40 years of age are rare, with men more likely to develop the disease than women. MM is twice as common in black populations compared with white and Asian ethnicities.[14]

MM patients experience a variety of disease-related events and subsequent disability, such as bone destruction leading to pain, height reduction and body shape changes, bone marrow failure, renal failure, immunodeficiency, and the psychosocial burden of a diagnosis of cancer. These aspects may have different importance for the patient in different periods of the disease. Therapeutic interventions may also produce troublesome side effects and functional impairments.[15,16]

A similar psychosocial burden may be present in caregivers of MM patients, with the role and level of care required evolving as the disease progresses.[15] Health-related quality of life assessment tools that introduce the patient's perspective into the clinical process via standardised self-reports may add an additional dimension to traditional endpoints in both clinical trials and practice.[16]

CLINICAL NEED AND BURDEN OF DISEASE

MM although a rare disease, is the second most common haematologic malignancy.[17] In 2016 in the UK, MM was the 19th most common cancer accounting for about 2% of all new cancer cases.[18] More specifically, in England in 2017, the number of registrations for newly diagnosed cases of MM (IDC-10 code C.90) summed up to 5,034 of which 2,931 (about 59%) were men,

furthermore, around 56% of total number of cases registered were people aged over 70 and over.[19] In the UK in 2014-2016, on average each year more than 4 in 10 (44%) new cases were in people aged 75 and over.[c]

European age-standardised incidence rates in the UK are projected to increase from 11.12 per 100,000 observed age-standardised rate (equating to 5,500 observed cases) in 2014 to 12.38 projected aged-standardised rate (equating 8,888 projected cases) by 2035.[20]

Hospital episode statistics for England 2017-18 recorded a total of 139,605 finished consultant episodes (FCE), 134,697 admissions of which 123,651 were day cases for multiple myeloma and malignant plasma cell neoplasms (ICD-10 code C.90) as primary diagnosis.[21]

In the UK in 2016, myeloma was the 17th most common cause of cancer death accounting for a 2% of all cancer deaths.[22] More specifically for England and Wales in 2017 there were a total of 2,756 registered cases of death as undelaying cause MM (ICD-10 code C.90).[23]

European age-standardised mortality rates for the UK are projected to decrease from 5.94 per 100,000 observed rate (equating to 2,928 observed deaths) in 2014 to 4.92 per 100,000 projected rate (equating to 3,835 projected deaths) by 2035.[24]

Myeloma survival is improving and has quadrupled in the last 40 years in the UK.[22] The one-year and five-year net survival for adults diagnosed between 2012 and 2016 and followed up in 2017 in England for myeloma was 82.1% and 51.7 % respectively.[25] Patients with MM have the lowest quality of life and highest number of severe symptoms among the haematological malignancies.[26]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Myeloma is not considered a curable disease. The main aims of treatment are to reduce the number of malignant plasma cells (myeloma), and to bring the patient into remission for as long as possible with the best quality of life. Usually, patients respond well to first line therapy, and this period tends to be where most patients experience the greatest length of remission.[27]

The initial treatment for MM may be either:

- non-intensive (Autologous Stem Cell Transplant (ASCT) Ineligible) – for patients classified as frail due to advanced age (e.g. 65 years) or comorbidity or because they decline ASCT for other reasons (this is more common)
- intensive (ASCT Eligible) – for younger or fitter patients[28]

Both non-intensive and intensive treatment pathways involve taking a combination of anti-myeloma medicines, but intensive treatment involves high-dose melphalan followed by an ASCT.[27] The medicines usually include an alkylating agent, a steroid medicine, and either thalidomide or bortezomib.[28]

As well as the main treatments for multiple myeloma, patients may also need treatment to help relieve some of the problems caused by the condition such as:[28]

- painkillers – to reduce pain

[c] Information provided by Takeda UK Ltd based on data sourced on request from the National Cancer Registration and Analysis Service (requested August 2018), ISD Scotland (requested April 2018), Welsh Cancer Intelligence and Surveillance Unit, Health Intelligence Division, Public Health Wales, (requested February 2019) and the Northern Ireland Cancer Registry (requested April 2018).

- radiotherapy – to relieve bone pain or help healing after a bone is surgically repaired
- bisphosphonate medicine given as tablets or by injection – to help prevent bone damage and reduce the levels of calcium in the blood
- blood transfusions or erythropoietin medication – to increase red blood cell count and treat anaemia
- surgery – to repair or strengthen damaged bones, or treat compression of the spinal cord
- dialysis – may be required if develop kidney failure is developed
- plasma exchange – treatment to remove and replace plasma

CURRENT TREATMENT OPTIONS

In the UK, for patients that are currently on first line treatment but have not received an ASCT there is no current treatment option offered as a maintenance therapy.[29]

PLACE OF TECHNOLOGY

If licenced for this indication, ixazomib citrate would provide a maintenance therapy option for NDMM patients that are currently on first-line treatment but have not received an ASCT. It is important to recognise that, in line with the International Myeloma Workshop (IMW) Consensus, such ixazomib maintenance therapy is regarded as part of the first-line treatment because it is taken as part of a course of therapy that was planned from the outset by the clinician.[30]

CLINICAL TRIAL INFORMATION

Trial	**TORUMALINE MM4, NCT02312258, U1111-1160-1702, EudraCT-2014-001394-13; adults aged 18 and over; ixazomib citrate vs placebo; phase III**
Sponsor	Millennium Pharmaceuticals, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.
Status	Ongoing
Source of Information	Trial register[5,31]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, placebo-controlled
Participants	n=706; aged 18 and over; confirmed diagnosis of symptomatic (NDMM according to standard criteria; completed 6 to 12 months (+- 2 weeks) of initial therapy; documented major response (PR, VGPR, CR) according to the International Myeloma Working Group (IMWG) uniform response criteria, version 2011, after this initial therapy.
Schedule	Randomised to: • Ixazomib 3 milligram (mg), capsule, orally, once, on days 1, 8 and 15 in a 28-day cycle for cycles 1 through 4. Ixazomib 3 or 4 mg*, capsules, orally, once, on days 1, 8 and 15 in a 28-day cycle for cycles 5 through 26. Participants experiencing adverse events (AEs) attributed to study drug during any cycle may continue in the study but may have doses of study drug held or reduced by at least 1 dose level. Reduced doses are: 3 mg, 2.3 mg, 1.5 mg and discontinuation of study drug. • Ixazomib placebo-matching 3 mg capsule, orally, once on days 1, 8 and 15 in a 28-day cycle for cycles 1 through 4. Ixazomib placebo-

	matching 3 or 4 mg capsules*, orally, once on days 1, 8 and 15 in a 28-day cycle for cycles 5 through 26. Participants experiencing AEs attributed to study drug during any cycle may continue in the study, but may have doses of study drug held or reduced by at least 1 dose level. Reduced doses are: 3 mg, 2.3 mg, 1.5 mg and discontinuation of study drug. *Upon evaluation of ixazomib toxicities at the completion of cycle 4, and on the basis of the dose escalation criteria outlined below, the study drug dose will be escalated to 4 mg beginning with cycle 5 day 1 and administered on the same schedule for the duration of the study to provide maximum possible clinical benefit for patients who tolerated the first 4 cycles of treatment. To provide patients the opportunity to derive maximum clinical benefit from study drug maintenance, the dose of 3 mg will be increased to 4 mg at Cycle 5 provided that, during the most recent 2 cycles (Cycle 3 and 4), there have been no non-hematologic AEs ⩾Grade 2 related to study drug, no dose interruptions related to study drug toxicities, and no delays of greater than 1 week in starting a cycle due to study drug toxicities. Patients who have had any dose reductions will not dose escalate. If dose escalation was inadvertently missed at Cycle 5, escalation at a later cycle may be performed with permission from the Millennium project clinician or designee.[d]
Follow-up	Active treatment for up to 26 cycles (28 day cycles), overall follow up to 104 months
Primary Outcomes	• Progression Free Survival (PFS) [Time Frame: From the date of randomization every 4 weeks during follow-up until progressive disease (PD) or death (Up to approximately 76 to 104 months)]
Secondary Outcomes	• Overall Survival (OS) [Time frame: from the date of randomization every 12 weeks after PD on next-line therapy until death (up to approximately 76 to 104 months)] • Percentage of Participants who Achieve or Maintain any Best Response Category During the Treatment Period [Time frame: up to 24 months] • Time to Progression (TTP) [Time frame: from the date of randomization to the date of first documented PD (up to approximately 76 to 104 months)] • Progression Free Survival 2 (PFS2) [Time frame: from the date of randomisation to every 12 weeks until 2nd PD or death (up to approximately 76 to 104 months)] • Time to Next Line Therapy (TTNT) [Time frame: from the date of randomisation to the date of the first dose of the next-line of therapy (up to approximately 76 to 104 months)] • Time to end of the Next-line of Therapy After Study Treatment [Time frame: from the date of randomisation to the date of last dose of the next-line of therapy (up to approximately 76 to 104 months)] • Duration of Next-line Therapy [Time frame: from the date of the first dose of the line of antineoplastic therapy coming after study treatment to the date of the last dose (up to approximately 76 to 104 months)]

[d] Information provided by Takeda UK Ltd

	• Percentage of Participants Who Develop A New Primary Malignancy [Time frame: from the randomisation date till death or termination of the study (up to approximately 76 to 104 months)] • Percentage of Participants with Conversion from Minimal Residual Disease (MRD) positive to MRD negative, or the Maintenance of MRD negativity [Time frame: screening, cycle 13, and cycle 26 (cycle length is equal to [=] 28 days)] • Correlation of MRD Status With PFS and OS [Time frame: screening, cycle 13, and cycle 26 (cycle length=28 days)] • OS in a High-risk Population [Time frame: from the date of randomisation to every 12 weeks after PD on next-line therapy until death (up to approximately 76 to 104 months)] • PFS in a High-risk Population [Time frame: from the date of randomisation to every 4 weeks during follow-up until PD or death (up to approximately 76 to 104 months)] • Eastern Cooperative Oncology Group (ECOG) Performance Status [Time frame: cycle 2 and every 28 days (up to 24 months) (cycle length =28 days)] • Percentage of Participants with Serious Adverse Events (SAEs) and Adverse Events (AEs) [Time frame: frst dose of study drug through 30 days after last dose of study drug (up to 25 months)] • Change From Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) [Time frame: baseline and every 28 days (up to 24 months)] • Number of Participants with any Markedly Abnormal Standard Safety Laboratory Values [Time frame: from first dose date of study drug through 30 days after the last dose of study drug (up to 25 months)] • Correlation between Frailty Status and PFS and OS [Time frame: up to approximately 76 to 104 months] • Pharmacokinetic Parameter: Plasma concentration of Ixazomib [Time frame: cycle 1 (1 and 4 hours post-dose day 1, days 8 and 15 pre-dose); cycle 2 and 5 (days 1 and 8 pre-dose) and cycles 3, 4, 6-10 (day 1 pre-dose) (cycle length =28 days)] • Time to Resolution of Peripheral Neuropathy (PN) Events [Time frame: from the initial onset date of PN up to the resolution date for resolved events (up to 25 months)] • Time to Improvement of PN Events [Time frame: from the initial onset date of PN up to the improvement of event (up to 25 months)]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as August 2019, study completion date reported as October 2024.

ESTIMATED COST

The NHS List price of Ninlaro (ixazomib citrate) capsules 2.3 mg, 3 mg. and 4 mg. is £6,336 for a pack of 3 capsules.[32]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guideline. Myeloma: diagnosis and management (NG35). February 2016.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation. NHSCB/B04/P/A. April 2013.

OTHER GUIDANCE

- National Comprehensive Cancer Network. Clinical Practice Guideline in Oncology: Multiple Myeloma. 2018.[33]
- Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2017.[34]
- International Myeloma Working group. Revised international staging system for multiple myeloma: a report from the International Myeloma Working Group. 2015.[35]
- British Committee for Standards in Haematology (BCSH) and the UK Myeloma Forum. Guidelines for the diagnosis and management of multiple myeloma 2014.[36]
- European Myeloma Network. European Myeloma network recommendations on the evaluation and treatment of newly diagnosed patients with multiple myeloma. 2014.[37]

ADDITIONAL INFORMATION

Millennium Pharmaceuticals, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.[38]

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